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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,297	02/17/2004	Apollon Papadimitriou	20619US1	9601

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,297	PAPADIMITRIOU, APOLLON	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18,22-37 and 39-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18,22-37 and 39-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/853,731.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/20/06 & 2/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on January 17, 2006 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1-16, 18, 22-37 and 39-68 are pending.

The pending claims were allowed on September 12, 2005. However, the instant application was withdrawn from issue, and applicants have filed RCE and submitted IDS to be considered. Thus, claims 1-16, 18, 22-37 and 39-68 are examined.

Priority

3. The instant application is a continuation of U.S. Application 09/853,731, filed May 11, 2001, which claims the priority of EP 00110355.5, filed May 15, 2000. However, the EP document does not disclose methionine as an antioxidant for the claimed composition, thus, the priority date of the claimed composition comprising methionine is the effective filing date of parent application, May 11, 2001.

Information Disclosure Statement

4. Applicants' IDS filed January 20 and February 16 are acknowledged. Most of the references listed on the IDS and the Opposition filed by Sandoz against European Patent EP1311285 (which corresponds to the instant application) have been considered, one reference Austria Codex 1998/99 is not considered because it is not written in English.

Withdrawn Claim Rejections-Obviousness Type Double Patenting

5. The previous rejection of claims 1, 18, 22, 39 and 49-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of

copending Application No. 10/014,363, is withdrawn in view of cancellation of claims 1-16 in the amendment of 10/014,363 filed November 25, 2005.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5, 9-16, 18, 22-26, 30-39, 46-52 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailon (U.S. Patent No. 6,583,272, effective filing date, July 2, 1999) in view of Takuri (U. S. Patent 5,272, 135) as evidenced by Papadimitriou (U.S 2004/0147431).

Bailon teaches a conjugate comprising an erythropoietin (EPO) glycoprotein having at least one free amino group and having the in vivo biological activity and a poly(ethylene glycol) (peg) group; and a pharmaceutical composition comprising the conjugate and a pharmaceutically acceptable carrier (column 2, line 56-column 3, line 6; column 3, lines 41-47), wherein the EPO glycoprotein is selected from the group consisting of human EPO and analogs thereof which have sequence of human EPO such as SEQ ID NO:1 or 2 (claims 12, 33), modified by addition of 1 to 6 glycosylation sites or a rearrangement of at least one glycosylation site, e.g., the modification sequence $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ (column 5, line 28-column 6, line 5; claims 13-16, 34-39) and the glycoprotein is covalently linked to "n" peg groups of the formula –CO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR, where R is lower alkyl; x is 2 or 3; m is about 450-900; n is 1-3; and n and m are chosen such that the molecular weight of the conjugate minus the glycoprotein is from 20 kDa to 100 kDa (column 2, line 56-column 3, line 6; column 3, line 48-column 4, line 4;

Table 3; claims 18, 49-52). The peg-EPO is prepared in various formulations (Table 3; Example 8), e.g., formulation C containing 10 or 100 μg/ml peg-EPO, 10 mM (corresponding to 1.38 mg/ml) phosphate, 140 mM sodium sulfate, pH 6.2; formulation D containing 10 or 100 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate (corresponding to 5.68 mg/ml), pH 6.2; formulation E containing 50 or 400 μg/ml peg-EPO, 10 mM phosphate, 100 mM sodium chloride, pH 7.0; formulation G containing 400 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate, 3% mannitol (w/v), pH 6.2 (claims 1-5, 9-11, 22-26, 30-32, 46-48 and 59). However, Bailon does not disclose the use of methionine as an antioxidant in the pharmaceutical composition.

Takuri teaches the addition of methionine to a liquid or semi-solid medium containing a polypeptide (e.g., a hormone) having at least one methionine residue in an amount effective to inhibit the oxidation of the methionine residue (column 1, lines 6-16; column 2, lines 32-43, 60-68), where the polypeptide encompasses natural, synthetic, recombinant or modified polypeptide having a desired biological activity, the amount of methionine is about 0.01% (w/v) to about 1.0% (w/v), the medium contains buffer such as phosphate and sodium chloride, and the pH of the buffer can be about 7.0 to about 7.4 (column 3, lines 34-39; column 4, lines 29-42, 42-55; column 6, lines 7-8). Although Takuri does not specifically indicate the polypeptide is EPO, which has a methionine in its peptide sequence as evidenced by Papadimitriou (U.S 2004/0147431; Example 11), Takuri discloses the polypeptide can be modified and can be a methionine-containing hormone, where the addition of methionine to the pharmaceutical composition would inhibit the oxidation of the methionine residue in the polypeptide and prolong the half-life of the polypeptide.

At the invention was made, it would have been obvious that one of ordinary skill in the art is motivated to add methionine as taught by Takuri to the pharmaceutical composition comprising EPO-PEG conjugate as taught by Bailon because addition of methionine to the pharmaceutical composition comprising EPO conjugate would increase the stability of EPO conjugate and the prolong the half-life of the EPO conjugate in the pharmaceutical composition. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

7. Claims 1-16, 18, 22-39, 46-52 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailon (U.S. Patent No. 6,583,272, effective filing date, July 2, 1999) in view of Sato (WO 00/51629, published on September 8, 2000) based on the English Equivalent patent (U. S. Patent 6,908,610).

Bailon teaches a conjugate comprising an erythropoietin (EPO) glycoprotein having at least one free amino group and having the in vivo biological activity and a poly(ethylene glycol) (peg) group; and a pharmaceutical composition comprising the conjugate and a pharmaceutically acceptable carrier (column 2, line 56-column 3, line 6; column 3, lines 41-47), wherein the EPO glycoprotein is selected from the group consisting of human EPO and analogs thereof which have sequence of human EPO such as SEQ ID NO:1 or 2 (claims 12, 33), modified by addition of 1 to 6 glycosylation sites or a rearrangement of at least one glycosylation site, e.g., the modification sequence $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ (column 5, line 28-column 6, line 5; claims 13-16, 34-39) and the glycoprotein is covalently linked to "n" peg groups of the formula –CO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR, where R is lower alkyl; x is 2 or 3; m is about 450-900; n is 1-3; and n and m are chosen such that the molecular weight of the conjugate minus the glycoprotein is from

20 kDa to 100 kDa (column 2, line 56-column 3, line 6; column 3, line 48-column 4, line 4; Table 3; claims 18, 49-52). The peg-EPO is prepared in various formulations (Table 3; Example 8), e.g., formulation C containing 10 or 100 μg/ml peg-EPO, 10 mM (corresponding to 1.38 mg/ml) phosphate, 140 mM sodium sulfate, pH 6.2; formulation D containing 10 or 100 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate (corresponding to 5.68 mg/ml), pH 6.2; formulation E containing 50 or 400 μg/ml peg-EPO, 10 mM phosphate, 100 mM sodium chloride, pH 7.0; formulation G containing 400 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate, 3% mannitol (w/v), pH 6.2 (claims 1-11, 22-32, 46-48 and 59). However, Bailon does not disclose the use of methionine as an antioxidant in the pharmaceutical composition.

Sato teaches a stabilized composition containing a physiologically active protein having a methionine residue, further containing methionine and one or more other amino acids, where the addition of methionine inhibits the protein from producing a variant oxidized at methionine residue, and wherein the physiologically active protein can be granulocyte colony-stimulating factors (G-CSF), EPO or PTH (column 3, lines 16-20, 36-40; column 8, lines 14-41), the amount of methionine is about 0.001-5 mg/ml, and the composition contains buffer such as phosphate and citrate (column 5, lines 12-20; column 6, lines 47-54).

At the invention was made, it would have been obvious that one of ordinary skill in the art is motivated to add methionine as taught by Sato to the pharmaceutical composition comprising EPO-PEG conjugate as taught by Bailon because addition of methionine to the pharmaceutical composition comprising EPO conjugate would increase the stability of EPO conjugate in the pharmaceutical composition. Thus, the combined references result in the

claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-16, 18, 22-37 and 39-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 of copending Application No. 09/853,731 base on the amendment filed January 23, 2006. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-16, 18, 22-37 and 39-68 in the instant application disclose a liquid pharmaceutical composition consisting essentially of an EPO glycoprotein product having the in vivo biological activity, a multiple charged inorganic anion, a buffer at pH of 5.5 to 7.0 and methionine, where the EPO product can be a pegylated EPO product. This is an obvious variation in view of claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 in the copending application which disclose a liquid pharmaceutical composition comprising a pegylated EPO glycoprotein product having the in vivo biological activity, a multiple charged inorganic anion and a buffer at pH of 5.5 to 7.0, and the liquid

composition is stable at room temperature for at least 6 months; and the specification indicates an antioxidant such as methionine can be added to the composition (paragraph [0044]). Since both the claims of the instant application and the claims of the copending application are directed to a pharmaceutical composition comprising an EPO glycoprotein product such as pegylated EPO product, a multiple charged inorganic anion, a buffer at pH of 5.5 to 7.0 and methionine. Thus, claims 1-16, 18, 22-37 and 39-68 in present application and claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 in the copending application are obvious variations of a pharmaceutical composition comprising a pegylated EPO glycoprotein product having the in vivo biological activity, a multiple charged inorganic anion, a buffer at pH of 5.5 to 7.0 and methionine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
March 14, 2006